

Naval Submarine Medical Research Laboratory



NSMRL REPORT 1210

25 AUG 1998



A New Strategy to Address Loss of Submarine Qualifications in Submariners Who are *Helicobacter Pylori* Positive and Diagnosed with Peptic Ulcer Disease: Background to the Change in Policy

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19981002 002

Released by
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Background to the Change in Policy

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A handwritten signature in black ink, appearing to read "M. T. Wooster". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

M. T. Wooster
Commanding Officer
NavSubMedRschLab

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SUMMARY PAGE

PROBLEM:

It was USN policy to disqualify submariners from returning to submarine duty for two years following a peptic ulcer. This resulted in a loss of experienced personnel which was considered to be unnecessary given the current medical advances in peptic ulcer therapy. This is an evaluation of the medical literature to provide background to why the current USN policy of disqualifying submariners from submarine duty following the diagnosis of peptic ulcer disease has been changed.

FINDINGS:

The medical literature shows that infection with *Helicobacter pylori* is causally related to the majority of both duodenal and gastric ulcer cases. The second most common cause of peptic ulcer results from the use of non-steroidal anti-inflammatory drugs such as Ibuprofen (Motrin, Advil, etc). Repeated studies have demonstrated that eradication of *Helicobacter pylori* infection in patients with peptic ulcer disease results in a dramatic reduction of ulcer recurrence from as high as 74 to 95% to between 1.1% and 8%. This recurrence rate includes duodenal, gastric, and complicated ulcers. Re-infection with *Helicobacter pylori* is uncommon in western countries, with rates ranging between zero and 6.25% during the first year. Longer term studies reveal annual re-infection rates of 0.36% to 1.5%.

APPLICATION:

Results indicate that it is reasonable to return submariners to duty with a low expectation of complications contingent upon eradication of the bacteria *Helicobacter pylori* and complete healing of the peptic ulcer.

Acknowledgment and Disclaimer

This project was conducted under Naval Medical Research Development Command Research Work Unit 63706N-M0096.002-5205, "Medical Conditions Affecting Submarine Qualifications." The views expressed in this report are those of the authors and do not reflect the official policy of the Department of the Navy, Department of Defense, or the US Government. It was approved for publication on 25 Aug 1998 and designated NSMRL Report 1210. The author would like to extend thanks to all those who aided, critiqued, and otherwise helped in the preparation of this paper. In particular, thanks to LCDR Neal Carlson for editorial comments and Susan Monty for preparing the manuscript.

Background

Peptic ulcer disease (PUD) is a chronic inflammatory condition of the stomach and duodenum that affects 10% of people in the United States at some time in their lives, and has a point prevalence rate of 2% of the adult US population (1,2). Over the past fifteen years PUD has been variously attributed to stress, diet, decreased mucosal defenses, as being idiopathic in origin, and medications. Each new theory led to the development of novel therapies (i.e. antacids, H2 blockade and proton pump inhibition) which met with initial success, but in the main each failed. Thus recurrence rates are reported to be as high as 95% for duodenal ulcers and 74% for gastric ulcers (3).

Based on the "unpredictability and seriousness of the major complications of perforation, hemorrhage, and obstruction" (4) and the limited medical care available aboard submarines, prior US Navy policy required that submariners diagnosed with PUD be disqualified from submarine duty until they were ulcer-free for two years. From 1990 to 1996 COMSUBLANT/PAC medical data indicated that 53 US Navy submariners were disqualified from duty due to PUD (5). Of the 48 submariners disqualified for PUD from 1990 to 1995, 31 (65%) were of the rank E5 to E7. US Navy Bureau of Personnel records show that between 1 Jan 1996 and 1 Oct 1996 of the 212 men disqualified for medical reasons, 11% (6) were due to peptic ulcer disease. The monetary and readiness-related cost of training and replacing USN submariners disqualified by the former policy was, therefore, substantial.

Several recent advances in understanding the etiology and improved

management of the disease have markedly changed the prognosis of PUD (1, 3, 7-14) and justify the change of the disqualification policy. First, *Helicobacter (H.) pylori* infection has been noted in 95% of those afflicted with duodenal ulcers and 74% of those afflicted with gastric ulcers (8). Second, the *H. pylori* bacterium has been hypothesized and in some cases documented, to produce ulcers by mechanical, immunologic, and cytotoxic means (15-26). Third, *H. pylori* is readily eliminated with common antibiotics. Fourth, eradication of *H. pylori* infection results in a dramatic and persistent reduction in the recurrence rate of duodenal and gastric ulcers. As a result, eradication of *H. pylori* is now a major part of the accepted medical practice in the treatment of peptic ulcers.

The purpose of this report is to present evidence supporting the relaxation of the former US Navy policy of disqualifying submariners diagnosed with PUD. The argument is based on recent advances in the management of PUD, particularly the eradication of *H. pylori* which has markedly improved the prognosis of the disease by minimizing its recurrence. Specifically, this paper summarizes the current understanding of the characteristics, demographics, treatment, and prognosis of PUD associated with *H. pylori* infection. It also addresses the relevance of the dramatically reduced rate of recurrence of *H. pylori*-induced PUD demonstrated in civilian populations to the submarine community. Lastly, guidance for the medical management (diagnosis, treatment, and follow-up evaluation) of submariners with PUD is presented with clarification or justification for each element of the guidance. The ultimate result of instituting the guidance is an increase in the

retention of career submariners and a decrease in the associated retraining costs.

Peptic Ulcer Disease: Description and etiology

A peptic ulcer is a circumscribed erosion of the mucous membrane penetrating through the mucosa and superficial stomach musculature and occurs in areas exposed to acid. The natural history of peptic ulcer disease is one of chronicity and recurrence and occurs more frequently in males. The pathogenesis of ulcers has been radically re-examined with the discovery of *H. pylori*. Previously an excess of acid and gastrin (the hormone responsible for acid secretion) were considered the cause of most duodenal ulcers and the breakdown of mucosal defenses the cause for most gastric ulcers. Other suspected causes included stress, diet, medications, and endocrine diseases. More rare etiologies for ulcer include cancers such as lymphoma and sarcoma, with duodenal ulcers generally being benign, and gastric ulcer malignant (27).

Peptic Ulcer Disease: Symptoms and Complications

Symptoms vary with the ulcer's location and the patient's age; symptoms can be atypical and minimal. Only about 50% of patients present with the characteristic pattern of symptoms. Typically ulcer is associated with pain which is burning, gnawing or aching in character but may also be described as soreness, emptiness, or hunger. Pain is generally steady, located in a well-circumscribed area, usually epigastric, and is relieved by antacids or milk. In those with duodenal ulcer, typically the pattern of pain tends to be relieved by food but recurs two or three hours following a meal. The symptoms of gastric ulcer follow a different pattern and are generally unrelated to meals and the pain may be caused by food and not relieved by it.

The complications of peptic ulcer disease include perforation (rare), hemorrhage, which is found in up to 50% of civilian ulcers (28), and obstruction of the gastric outlet (occasionally found in gastric ulcers). The percent of bleeding ulcers in the submarine force has not been studied but it will be assumed to approximate that of the civilian literature. Except for bleeding, the complications secondary to ulcers are generally rare.

Peptic Ulcer Disease: Diagnosis

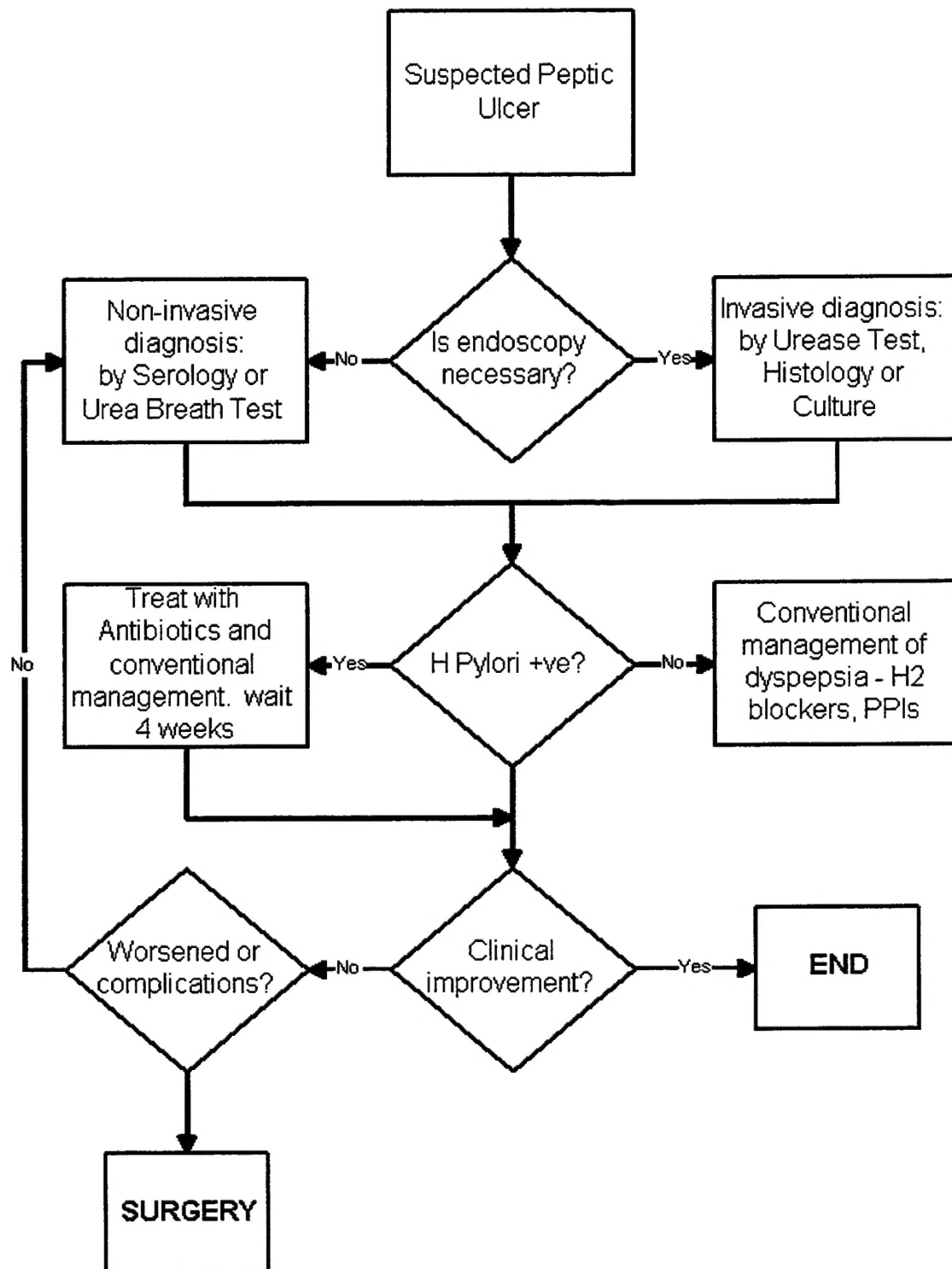
Diagnosis is suggested by the symptoms and confirmed by the studies described below. Endoscopy usually can establish the diagnosis and is useful for a number of reasons. First, it can detect shallow ulcers missed by radiologic contrast studies such as barium swallow. Second, the endoscope can reach places that are difficult to visualize via x-ray studies, such as the posterior stomach, duodenum, and surgical anastomosis. Lastly, endoscopy enables one to biopsy the ulcer to look for cancer and to test for *H. pylori* via the CLO test (a colorimetric test that relies on pH changes induced by the urease producing *H. pylori*) or culture. However, even in experienced hands up to 10% of ulcers can be missed by endoscopy (27). Barium studies, prior to endoscopy, were used to diagnosed ulcers, but given the high false negative rate and the exposure to radiation, this test has since become secondary (1, 27).

Peptic Ulcer Disease: Treatment

Treatment of gastric and duodenal ulcers, prior to knowledge about *H. pylori*'s role, was aimed at neutralizing or decreasing gastric acidity (even though gastric acidity is usually normal). This was accomplished by neutralizing acid with antacids, blocking the secretion of acid with H₂ receptor blocking agents or proton pump inhibition agents, or coating the stomach with a protective barrier

such as the medication sucralfate. Other medications used were anticholinergics and certain prostaglandins. Surgery is generally

reserved for intractable ulcers. Indications for surgery include perforation, obstruction, no response to medical therapy, major



hemorrhages, and malignancy. Figure 1 is an accepted algorithm for the medical treatment of dyspepsia or upper gastrointestinal problems (14, 29, 30). This algorithm is a diagram of information found in the consensus statement regarding the medical treatment of peptic ulcer disease drawn up by the Practice Committee of the American College of Gastroenterology in 1996 and an article by Dr Barry Marshall delineating the characteristics and relationship of *H. pylori* to peptic ulcer disease (14, 29).

In the past, anti-ulcer medications could only partially interrupt the natural history of ulcer disease (27). Prolonging treatment to greater than two years on antisecretory agents did not reduce the risk of relapse, which was up to 95% for duodenal ulcers, one year after stopping therapy. This led to the following options: retreat relapses, continue therapy indefinitely, or consider surgery. New insight was required before new treatment options could be explored and tested.

Helicobacter pylori: Description

Until recently PUD was not attributed to an infectious agent because the prevailing dogma was that the stomach was sterile and could not support bacteria. However, over the last 100 years, various medical journals have described an unidentified curved spiral bacterium that could be found in the stomach (31). The spiral bacterium was first isolated from gastric acid in 1886 originally was named *Campylobacter pylori* and has since been renamed *H. pylori* (31, 32). In the early 1980's Robin Warren at the Royal Perth Hospital in Western Australia discovered a spiral bacterium in the stomach of various patients with gastritis (31). In 1981, he and Barry Marshall, also of the Royal Perth Hospital, began a collaboration to attempt to culture the organisms that were

found in gastric secretions (33). In 1982, they began a prospective study of 100 patients undergoing endoscopy for gastric complaints (31). They obtained biopsy specimens for culture and staining and read the pathology sections blinded to any clinical details. The investigators hypothesized that the spiral bacteria was related to *Campylobacter* organisms (a spiral bacteria found in food, the gut of pets, and those with poor dental hygiene). Many different culture media were tried and after much trial and error, *H. pylori* was isolated and cultured using a microaerophilic blood-based medium (34, 35).

The bacterium survives in gastric acid by breaking down urea and generating an alkaline microenvironment for itself. *H. pylori* attaches only to the mucous-secreting gastric epithelial cells that line the stomach and in this location occupy a micro-aerophilic, pH-neutral environment at the junction between the mucosa and the lumen. Its spiral nature and corkscrew-like motility permit it to penetrate the mucous gel overlying gastric epithelium and to set up residence adjacent and adherent to gastric epithelium. Technically speaking, the organism does not invade the tissues. This may explain why the bacterium is not eradicated by normal immune responses (31).

Helicobacter pylori: Etiology

After identifying *H. pylori* in the stomach it was necessary to see if it was causally related to PUD. Robert Koch, a 19th century German physician and pioneering microbiologist, formulated the universally accepted criteria that provided proof that a specific bacterium caused a disease (36). In order to prove that *H. pylori* was the etiologic agent of human gastritis and ulcer, Marshall et al (37), and Morris

and Nicholson (38) independently satisfied Koch's four postulates:

1. The organism was known to be found in humans with gastritis and duodenal ulcer and was essentially absent in those without disease.

2. *H. pylori* was isolated from symptomatic patients and grown in pure culture.

3. Ingestion of the organism was associated with reproduction of the disease.

4. *H. pylori* was re-isolated from subjects who had ingested the organism.

This work conclusively demonstrated that there was an association between the disease state known as peptic ulcer disease and the bacterium *Helicobacter pylori*.

Helicobacter pylori: Pathogenicity

H. pylori pathogenicity has been attributed to mechanical, immunologic, and cytotoxic factors (15-26). The first step of infection involves colonization of the gastric mucosa. This is accomplished by specific

attachment of the organism to the human host as well as a urease enzyme (an enzyme which breaks down urea to ammonia) that creates a hospitable microenvironment. Once colonization has been established the pathogen must avoid the host immune response. This is accomplished by a protective enzyme, a catalase, which breaks down damaging reactive oxygen metabolites such as hydrogen peroxide, superoxide, and radicals subsequently protecting the organism from the immune systems phagocytic activity. Direct damage to the host may play a role. A phospholipase, vacuolating cytotoxin, and protease may supply nutrients to the organism by damaging the epithelial cells thereby increasing the solubility of mucous. These and other putative virulence factors are listed in Table 1.

Table 1. Factors that might enhance virulence and pathogenicity in *H. pylori*

<u>Factor</u>	<u>Comments/Action</u>
Spiral shape	Allows motility in mucous
Flagella	Efficient motility in mucous
Specific attachment to phosphatidyl ethanolamine, GM3 ganglioside Lewis B antigens	Selective colonization of gastric, mucous-secreting, epithelial cells
Urease	Survival in gastric environment, ammonia is toxic to epithelial cells in some animal models
Phospholipase	Digestion of epithelial cell membranes and mucous layer. Increased moistening of mucosa.
Catalase	Survival in gastric mucosa and possibly within phagocytic vacuole (protection from H ₂ O ₂)
Protease	Digestion of epithelial cell membranes and mucous layer. Increased solubility of mucous.
Vacuolating cytotoxin	Damage to epithelial cells, perhaps allowing egress of nutrients from submucosa
Low molecular weight chemo-attractant	Attraction of neutrophils and mononuclear proteins cells that release reactive oxygen species and interleukins

Helicobacter pylori: Relationship to Peptic Ulcer Disease

Once *H. pylori* had been associated causally with PUD an intense amount of research then ensued that demonstrated the reduction of ulcer recurrence with the successful treatment (eradication) of *H. pylori*. Various researchers have investigated the epidemiology and relationship of the bacterium to gastrointestinal disease (Table 2) (15-26, 31). Although *H. pylori* is prevalent in all populations studied (Figures 2 and 3), only a small proportion (1%) of infected persons will develop an ulcer during their lifetime (7, 31). However, almost all duodenal ulcers and the majority of gastric ulcers are associated with *H. pylori* infection. *H. pylori* infection has been noted in 95% of those afflicted with duodenal (the first part of the small intestine) ulcers and 74% of those afflicted with gastric ulcers (8). The proportion of gastric ulcer patients infected with *H. pylori* increases to 96%, if those with other recognized causes, i.e., those associated with non-steroidal anti-inflammatory drug (NSAID) use, or gastrinoma (a rare tumor that secretes excess amounts of the hormone gastrin, such tumors frequently occur in the pancreas) are excluded (9).

With the discovery of the link between an infectious agent and PUD, antibiotics entered the treatment armamentarium of physicians with dramatic results. Repeated studies (Table 2) have demonstrated that eradication of *H. pylori* infection in patients with PUD results in a dramatic reduction of the rate recurrence of duodenal, gastric, and complicated ulcers (3, 8, 12, 39, 40, 41). Graham et al. (3) demonstrated that following *H. pylori* eradication there was a lasting decrease in the recurrence of ulcers in 109 patients up to two years after healing of ulcers. Recurrence rates were 12% versus

95% for duodenal ulcer, and 13% versus 74% for gastric ulcer. Hentschel et al. (12) demonstrated that among patients given both antibiotic and antisecretory agents ulcer recurrence occurred in 8% versus 86% for those receiving antisecretory therapy alone. Ulcers recurred in only 2% of those who had *H. pylori* eradication versus 85% recurrence in those who did not have *H. pylori* eradication.

A study by Sung et al. (8) also supports the above premise. Among patients given antibiotics 92% had *H. pylori* eradication and 85% had ulcer healing; in the group receiving antisecretory therapy alone 13% had *H. pylori* eradication and 73% had ulcer healing. One year after treatment, 5% (1/22) of the antibiotic treatment group had ulcer recurrence versus 53% (12/23) of the antisecretory treatment group. A recent study by Van der Hulst et al. (41) in 141 patients with duodenal ulcers and 45 patients with gastric ulcers demonstrated that recurrence of PUD (excluding patients taking aspirin or NSAIDs) is completely prevented after successful *H. pylori* eradication for up to 9.8 years. These results demonstrated that the probability of recurrence for patients receiving various antibiotic therapies along with antisecretory therapy was significantly lower than for patients who received antisecretory therapy alone.

Three prospective trials have examined the effect of *H. pylori* eradication on ulcer recurrence and *H. pylori* recrudescence. Borody et al. (42) examined 94 patients with documented *H. pylori* eradication and ulcer healing four years following treatment. They determined that only 2.2% were *H. pylori* positive and that the effective re-infection rate was 0.36% per patient per year. Labenz et al. (39) determined that with successful *H. pylori* eradication the one year ulcer

Table 2.

Author	Year	Study Type	Publication	Number	Results
1) Graham et al.	1992	Follow-up of randomized controlled trial	Ann Int Med V 116 #9	109	Recurrent ulcer rates of those treated with H-2 agents 95% for DU, 74% GU; if treated with triple antibiotics, rates decrease to 12% DU, 13% GU; with documented <i>H. pylori</i> eradication, rate of recurrence is 8%.
2) Nomura et al.	1994	Case control	Ann Int Med V 120 #12	Cohort of 5443 JAP-AM males	Pre-existing <i>H. pylori</i> infection increases risk for subsequent development of DU/GU 92% for DU, 93% for GU.
3) Hentschel et al.	1993	Randomized case control	NEJM V 328 #5	104	Ulcer recurrence is 2% with successful <i>H. pylori</i> eradication.
4) Forbes et al.	1994	Retrospective double blind trial	Lancet V 343	100 Australians	92% of DU with <i>H. pylori</i> eradication remained <i>H. pylori</i> negative for 7.1 years.
5) Hyams et al.	1995	Prospective	Am J Trop Med V 52 #1	1000 males USN MC personnel	<i>H. pylori</i> prevalence 25% in recruits abroad and dependent upon demographics.
6) Barody et al.	1994	Prospective	AJG V 89 #10	94 Australians	<i>H. pylori</i> re-infection rate 0.36%; efforts to eradicate <i>H. pylori</i> are worthwhile and justified.
7) Labenz et al.	1994	Prospective	AJG V 89 #10	190	With successful <i>H. pylori</i> eradication 1 yr ulcer recurrence decreases from 67.9% to 1.1%; 3 yr ulcer recurrence decreases from 91.1% to 3.0%. The <i>H. pylori</i> re-infection rate, in the 1 st year is 2.6%, in 2 nd year is 1.2%, in 3 rd /4 th year is 0%. Overall re-infection rate is 1.5%.
8) Sung et al.	1995	Randomized case control	NEJM V. 332 #3	100	In patients with positive <i>H. pylori</i> infection and non NSAID PUD, one week of antibiotic treatment without acid suppression heals ulcers as well as omeprazole, and decreases recurrence. In Antibiotic group, ulcer recurrence is 4.5%. In Omeprazole group, ulcer recurrence is 52.2%
9) Hammermeister et al.	1992	Prospective	European J. Clin. Microbiol. Infect. Dis. V. 11 #1	64 German Submariners 135 French infantry controls 74 German Air Force controls	Submarine crews have increased <i>H. pylori</i> infection rate (by serology) compared to controls. Submarine crews had total IgG/IgA antibody to <i>H. pylori</i> in 38%. Air Force controls had total IgG/IgA antibody to <i>H. pylori</i> in 18.9%. Infantry controls had total IgG/IgA antibody to <i>H. pylori</i> in 20.0%.
10) Van der Hulst et al.	1997	Prospective	Gastroenterology V 113 #4	141 DU and 45 GU	Excluding patients taking aspirin or NSAIDs, recurrence of peptic ulcers is completely prevented after successful <i>H. pylori</i> eradication for up to 9.8 years.

DU = duodenal ulcer
GU = gastric ulcer

NEJM = New England Journal of Medicine
AJG = American Journal of Gastroenterology

USN = U S Navy
MC = Marine Corps

PUD = Peptic Ulcer Disease
NSAID = Non Steroidal Anti-Inflammatory Drug

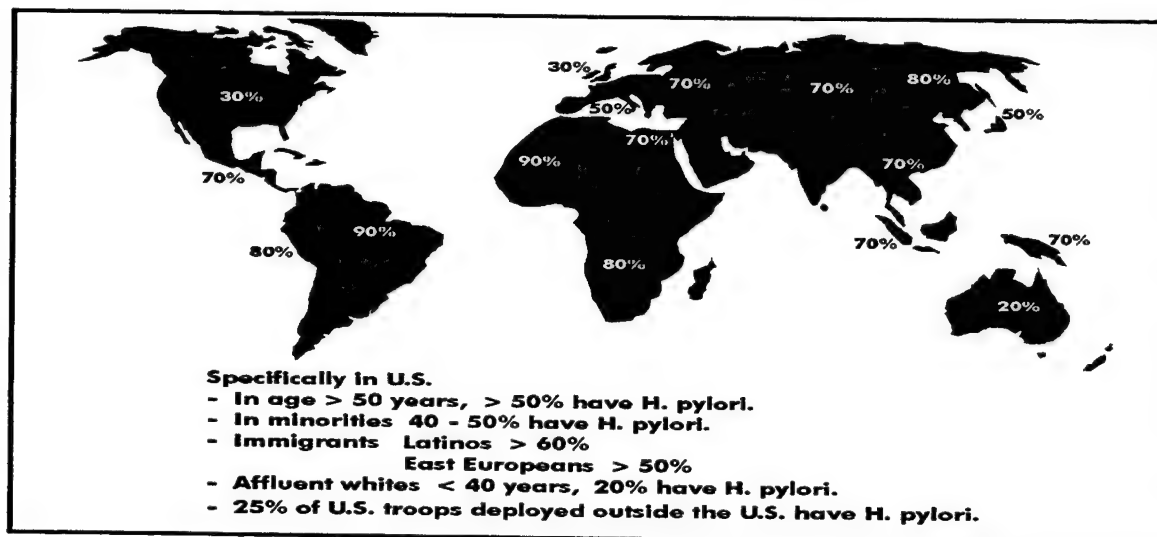


Figure 2. World wide prevalence of *H. pylori*

recurrence rate decreases from 68% to 1.1% and the three year ulcer recurrence rate decreases from 91% to 3%. In this study of 190 people, the *H. pylori* re-infection rate was 2.6% the first year, 1.2% the second year, and 0% in the third and fourth year. Overall the re-infection rate was 1.5%. Forbes et al (43), in a prospective double-blind trial found that 92% (32/35) previously rendered *H. pylori* negative remained negative after 7.1 years. Duodenal ulceration was found in 20% (5/25) of patients found *H. pylori* positive, compared to 3% (1/38) of *H. pylori* negative patients.

The strongest argument supporting a change in the disqualification policy toward those with ulcers is the decreased risk of gastrointestinal hemorrhage following peptic ulcer disease healing and *H. pylori* eradication. Peptic ulcers are the most common cause of acute hemorrhage in the upper gastrointestinal tract, accounting for about 35% to 50% of cases (44, 45). Recently, a review article by Jaspersen examined the occurrence of acute gastrointestinal hemorrhage following *H. pylori* treatment (44). He found a number of studies that indicate a reduced risk of acute

gastrointestinal hemorrhage with successful *H. pylori* eradication: Graham et al (46) randomized 31 patients with upper gastrointestinal bleeding ulcers and found that after successful *H. pylori* eradication the recurrence of bleeding was 0%. Labenz et al

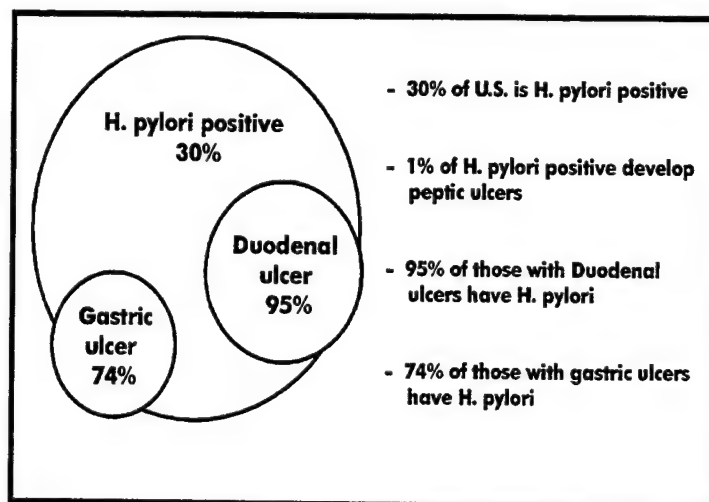


Figure 3. Relationship between *H. pylori* and Peptic Ulcer Disease

Table 3. Methods of diagnosing *H. pylori* (69-75)

<u>Method</u>	<u>Specimen</u>	<u>SENS/SP</u> <u>EC</u>	<u>Comments</u>
Quick Serology/ CLO test	Biopsy/Serum	95% / 85%	<u>Advantages:</u> Performed in 10 minutes. Gives qualitative answer. Can exclude or confirm <i>H. pylori</i> . <u>Disadvantages:</u> Is a local test therefore if correct area not biopsied may miss diagnosis; an invasive test
Quick saliva test	Saliva (detect IgG)	90% / 85%	Same as quick serology
ELISA tests	Serum	95% / 95%	<u>Advantages:</u> Provides a quantitative titer; is a true test for urease producing organisms; appropriate for serial measurements. <u>Disadvantages:</u> Titer falls with variability (12-18 mo.).
Urease breath test	Breath sample	95-98% / 95-98%	<u>Advantages:</u> A global test of gastric mucosa; noninvasive; independent of antibody titer; is a true test for urease producing organisms; appropriate for serial measurements. <u>Disadvantages:</u> More complex; requires special instruments; ¹³ C test is expensive, ¹⁴ C test uses radioisotopes; false negatives occur if test performed close to antibiotic or antacid treatment.
Urease test of biopsy	Mucosal biopsy	90-95% / 98%	<u>Advantages:</u> Simple; quick; inexpensive. <u>Disadvantages:</u> Invasive; not suited for serial testing.
Histology	Mucosal biopsy	98% / 98%	<u>Advantages:</u> Simple; quick; accurate; provides a permanent record. <u>Disadvantages:</u> Invasive; not suited for serial testing.
Culture	Mucosal biopsy	90-95% / 100%	<u>Advantages:</u> 100% specific; may guide antibiotic therapy. <u>Disadvantages:</u> Invasive; not suited for serial testing.
Culture of stool	Stool sample	30-50% / 100%	<u>Advantages:</u> 100% specific; may guide antibiotic therapy <u>Disadvantages:</u> Low sensitivity
PCR	Stool, gastric juice, or mucosal sample	95% / 95%	<u>Advantages:</u> None presently. <u>Disadvantages:</u> Experimental; false positive reaction limit use.

(47) prospectively followed 66 *H. pylori*-positive patients with upper gastrointestinal bleeding ulcers and found after a median period of 17 months that the rebleeding rate was 0% with successful *H. pylori* eradication. Studies by Rokkas et al (48) and Jaspersen et al (28) reported similar results. At the time of writing this review there were no published articles indicating that ulcer rebleeding following *H. pylori* eradication is increased or demonstrates significant recurrence.

No published studies have been conducted regarding the epidemiology of *H. pylori* in the US submarine community, however, two studies have examined *H. pylori* in the military. In the first, a prospective study conducted by Hammermeister et al., (49) a statistically significant increase in the prevalence of antibodies (IgG and IgA) to *H. pylori* was observed in German submariners (38.1%) compared to controls (20%). Among the assumed risk factors for submariners were the crowded conditions and the limited sanitary facilities in their small, conventional boats. In the second, a prospective study conducted by Hyams et al., (50) a 25% *H. pylori* prevalence was found in US Marine Corps personnel. This prevalence was higher than expected for the demographics of the study population and indicate that deployed military personnel may be at increased risk for *H. pylori* infection.

Helicobacter pylori: Diagnosis

The finding of a causal relationship between *H. pylori* emphasized the importance of accurately diagnosing and characterizing the organism. Numerous validated methods to diagnose patients with *H. pylori* are available (Table 3). The choice of a test is a balance among the ease of use,

cost, accuracy, safety, and ease of obtaining the sample to be tested - i.e. whether it is invasive or non-invasive (51-57). The two main categories are invasive procedures, such as endoscopy, and noninvasive assays such as the urea breath test and serology. Invasive tests have been considered the "gold standard", but because they are more local than global they may be less accurate due to the patchy nature of some *H. pylori* infections (30). Additionally, endoscopy is more time-consuming and less cost-efficient than either the breath test or serology.

Table 3 summarizes the advantages and disadvantages of the various non-invasive tests for *H. pylori*. We propose that the urease breath tests be used as they do not rely on antibody titers (which are variable in magnitude and may not reflect current infection), do not require withdrawal of blood, and can be performed serially. As Table 3 shows, the CLO test, quick saliva test, and ELISA tests have similar advantages and disadvantages to each other. The disadvantages as compared to the breath tests are a higher risk of false negative and false positive results.

We proposed that a non-invasive method for annually following those with *H. pylori* be considered as it is easier, less expensive, safer, and can be shown to have similar sensitivity and specificity as endoscopy (see Table 3). The initial diagnosis should be made by endoscopy as it has the advantages of examining the anatomy, obtaining biopsy specimens for *H. pylori* culture, and treating active bleeding by cauterization.

Helicobacter pylori: Carbon Isotope Urea Breath Test

H. pylori manages to survive in the acidic environment of the stomach by converting urea into bicarbonate and ammonium to create its own alkaline "safe

zone." Clinicians can take advantage of this reaction by having patients ingest urea containing labeled carbon, an isotope of carbon that can be detected with instruments. In the presence of *H. pylori* most of the labeled urea is metabolized to produce labeled carbon dioxide while in the absence of the bacteria most of the urea is excreted intact in the urine (58). Therefore, the presence of an appropriate amount of labeled carbon in the carbon dioxide of a patient's breath is indicative of *H. pylori* infection.

There are two types of carbon isotope-urea breath tests. One of the urea breath tests uses the ^{13}C isotope (^{13}C -UBT). The other test uses the unstable, radioactive ^{14}C isotope (^{14}C -UBT). Both tests have been studied extensively and have high reported sensitivities and specificities (30, 59-69). It should also be noted that results of both ^{13}C and ^{14}C urea breath tests can be adversely affected by proton pump inhibitors (omeprazol), bismuth containing medications (Pepto-Bismol), and antibiotics, all of which can lead to false negative outcomes. A post therapy time interval of four weeks is necessary to allow for accurate confirmation of *H. pylori* eradication (65, 69). False negative results can be caused by administration of carafate (an anti-ulcer medication) or prevastatin (cholesterol lowering medication) within one week prior to the test, antacids or H2 blockers within twenty four hours prior to the test, and a failure to fast for six hours prior to the test (69).

The advantages of the ^{13}C -UBT include the use of a stable, nonradioactive isotope and its ability to accurately quantify gastric mucosal urease. However, because ^{13}C comprises only 1.1% of all carbon in nature and because the ratio of ^{13}C to ^{12}C in the expired breath varies with diet and exercise,

a relatively large dose of ^{13}C -urea is necessary to measurably increase $^{13}\text{CO}_2$ excretion. Ingestion of a test meal is necessary to delay gastric emptying of the labeled urea, allow time for the reaction to proceed, and for the labeled carbon to be absorbed by the digestive mucosa. Additionally, the ^{13}C -UBT requires the use of an isotope ratio mass spectrometer to determine the amount of labeled CO_2 expired (65).

The ^{14}C -UBT takes less time and costs less to perform. Hydrolysis of ^{14}C labeled urea peaks 10 to 20 minutes after ingestion, negating the necessity of a test meal and producing results much sooner than if the ^{13}C labeled urea is used (60). The main drawback of using the ^{14}C isotope is its unstable, radioactive nature but this hazard can be considered negligible except for pregnant women and children. It should be noted at this time that only the ^{13}C urease breath test has been approved by the Federal Drug Administration.

Urease Breath Test: Sensitivity and Specificity

Both the ^{13}C and ^{14}C labeled urea breath tests have reported sensitivities and specificities in the 90 to 100% range with mean values of 96 and 97%, respectively (30, 59). Such high values compare extremely favorably with other tests used to diagnose *H. pylori* infection including both invasive and noninvasive tests (Table 3) (51-57). Chronic inflammation and Warthin-Barry staining of gastric antral biopsy specimens are generally considered to be the most accurate diagnostic methods but both are invasive techniques that require more time to perform and are much more costly (30). The urea breath test, as well as IgG and IgA serology tests, are noninvasive, less costly, and less time consuming while

producing results that are not significantly different from the more invasive tests.

Urease Breath Test: Radiation and safety concerns

Proponents of the ^{13}C urea breath test have promoted its stable, nonradioactive nature, even though it is more difficult and more expensive than the ^{14}C version. Most of the safety concerns regarding the ^{14}C -UBT center around the long half life of the radioactive isotope used. Because of this long half life, the activity of the ^{14}C isotope is regarded as constant while present in the body (58). Moreover, because ^{14}C -urea does not have a major route of entry into metabolic pathways and is rapidly excreted as either $^{14}\text{CO}_2$ in the breath or as unchanged ^{14}C -urea in the urine, this concern is of little practical relevance (58, 60).

Despite the lack of a major entry point into metabolic pathways, there is ample evidence that a health concern is still unjustified based on direct radiation exposure. In the United Nations Scientific Committee on the Effects of Atomic Radiation 1988 Report, the global mean effective dose equivalent an average person receives from natural sources was reported to be 240 mrem per year (70). The largest calculated effective dose equivalent for the ^{14}C -UBT is 8 mrem or 1/30 that of the amount of natural radiation received annually (58). Therefore, the greatest effective dose equivalent ever received from

a ^{14}C -UBT delivers the same amount of radiation as would be received naturally in twelve days. Another study found that two days worth of natural radiation provides a greater dose equivalent to bone marrow and gonads than a ^{14}C -UBT (58). It was also found that a single upper GI X-ray series delivers more radiation exposure to bone marrow than 100 ^{14}C -urea breath tests (60). It should also be noted that a normal person carries 0.07 microCi of naturally occurring ^{14}C within their body tissues which is the equivalent of 1/14 of a ^{14}C -urea breath test (69). With all the supporting data, it is reasonable to conclude that the few diagnostic breath tests that one may receive will not provide a significant exposure to radiation.

Table 4 compares the radiation dose (in mrem) of a 1 microCi ^{14}C microdose given to a *H. pylori* positive man to that of several other common sources of radiation (60, 69). As the table shows, a single microdose (which uses a mere 1 microCi instead of the usual 1 to 5 milliCi) of ^{14}C -urea actually provides less radiation than is absorbed by a day's worth of sunlight. It is also much less hazardous than other commonly used diagnostic tests such as the chest X-ray and the upper GI series.

Urease Breath Test : Administration of ^{13}C -UBT

Prior to receiving the ^{13}C -urea breath

Table 4. Radiation dose (in mrem) of 1 microCi of $^{14}\text{CO}_2$ urease compared to common sources of radiation

<u>Tissue</u>	<u>1 Ci $^{14}\text{CO}_2$</u>	<u>Chest X-ray</u>	<u>Upper GI</u>	<u>1 day Natural</u>
Bone	0.22	-	-	0.35
lungs	0.01	4.0	476.0	0.35
Thyroid	0.24	61.5	7.0	0.35
marrow	0.32	3.0	114.0	0.35
Testes	0.24	<0.01	0.4	0.35

test, patients undergo an overnight fast and are then given a fatty or high carbohydrate meal, such as pudding, to slow gastric emptying. A baseline breath sample is taken and the labeled urea is administered. A typical dose is 125-150mg ^{13}C -urea mixed with water (30, 60, 66). A second breath sample is taken sixty minutes after the ^{13}C ingestion and is analyzed by an isotope ratio mass spectrometer. *H. pylori* infection is indicated when the value of ^{13}C for the second exceeds the baseline ^{13}C levels by 0.24% (30, 66).

Urease Breath Test : Administration of ^{14}C -UBT

Following an overnight fast, a mixture of ^{14}C labeled urea and tap water is ingested by the patient. The dosage of ^{14}C used varies from 1 to 5 milliCi depending on the source (59, 60, 71) but will be relatively small regardless. Breath samples are taken at 0, 10, 20, and 30 minutes by exhaling through a membrane containing straw into a benzethonium chloride or methanol containing vial. Results are assessed in a scintillation beta counter and can either be expressed as counts per minute (cpm) or disintegrations per minute (dpm). If cpm are used as the units then a mean value of 4398cpm (SD +/- 2468) per mmol of CO_2 is expected in a sample taken 20 minutes after ingestion in an *H. pylori* infected individual. Conversely, those not infected by the bacterium will have a mean value of 340cpm (SD +/- 196) per mmol of CO_2 (60). If dpm are used as the units then an increase of 200dpm or more over baseline values is considered to be positive, an increase less than 100dpm is considered negative, and an increase of 100 to 200dpm is considered inconclusive and a second trial is recommended (59, 67). Additionally, a study conducted by German researchers found that a ^{14}C -UBT can be considered to be positive if a patient exhales more than 2%

of the oral ^{14}C test dose within 60 minutes (72).

A relatively new method for administering the ^{14}C -UBT has been developed and involves the ingestion of the isotope in the form of a quickly dissolving capsule. This technique protects the urea from exposure to the bacterial flora of the oropharynx and insures that hydrolysis of the urea is due solely to the presence of *H. pylori* in the stomach. Therefore, the test can be done with a microdose (1 microCi) of the isotope and with a single breath sample (67, 68).

To perform the microdose test, fasting patients ingest a ^{14}C -urea capsule with 20mL of water. Ten minutes after administration, the patients hold their breath for ten seconds to insure adequate carbon dioxide content of the sample and then blow through a straw into a 2L aluminized balloon. One mmol of carbon dioxide is removed from the balloon and assayed for beta activity using a scintillation counter (67).

It was suggested that the ^{13}C -urea breath test be used to diagnose and serially follow *H. pylori* status in submariners for the following reasons. First, it is currently the only FDA approved urease breath test, and second, it does not require ingestion of any radioactive labeled urease. If the ^{14}C -urease breath test is FDA approved this decision can be re-evaluated.

Helicobacter pylori: Treatment

Currently there are a number of recommended and highly effective drug regimens available to treat *H. pylori* infected people (1, 14, 73). Because drug resistance evolves and drug regimens change a specific antibiotic recommendation will not be made. As long as the standard of care is followed and the *H. pylori* infection is eradicated, the specific medications used will be up to the

Table 5. FDA-Approved treatment options for *Helicobacter pylori* as of Sept. 1997 (73)

1. Omeprazole 40 mg QD and clarithromycin 500 mg TID for 2 weeks, then omeprazole 20 mg QD for 2 weeks.
2. Ranitidine bismuth citrate d(RBC) 400 mg BID and clarithromycin 500 mg TID for 2 weeks, then RBC 400 mg BID for 2 weeks.
3. Bismuth subsalicylate 525 mg QUD and metronidazole 250 mg QID and tetracycline* 500 mg QID for 2 weeks and H2 receptor antagonish therapy as directed for 4 weeks.
4. Lansoprazole 30 mg BID and amoxicillin 1 g BID and clarithromycin 500 mg BID for 2 weeks.
5. Lansoprazole 30 mg TID and amoxicillin 1 g TID for 2 weeks.

QD = once a day, BID = twice a day, TID = three times a day, QID = four times a day

*Although not FDA approved, amoxicillin has replaced tetracycline for patients in whom tetracycline is not recommended. Tetracycline not for use in children < 12 years.

Table 6. Antibiotic doses

Bismuth Subsalicylate (B)	Tetracycline (T)	Metronidazole (M)	Clarithromysin (C)	Amoxicillin (A)	Omeprazole (O)
QID	QID	QID	BID or TID	QID	BID
2 Tablets 4x	500 mg 4x	250mg 4x	500mg 2x or 3x	500mg 4x	20mg 2x
daily with meals and at bedtime	daily with meals and at bedtime	daily with meals and at bedtime	daily with meals	daily with meals and at bedtime	daily with meals

BID = two times a day, TID = three times a day, QID = four times aa day,

Table 7. Drug combinations and *Helicobacter pylori* cure rates

<u>Drug Combination (duration)</u>	<u>95% Confidence Intervals</u>	
BMT (1 week)	86 - 90%	76
BMT (2 weeks)	88 - 90%	77, 78, 79
BMT and O (1 week)	94 - 98%	77
BMA (1 week)	75 - 81%	77
BMA (2 weeks)	80 - 86%	77
MOC (1 week)	87 - 91%	12, 55, 76
AOC (1 week)	86 - 91%	12, 55
MOA* (1-2 week)	77 - 83%	12, 55

* amoxicillin 1g 2 x daily

Adapted from Soll AH. Consensus Statement: Medical Treatment of Peptic Ulcer Disease, Practice Guidelines. JAMA 1996 275; 622-629.

discretion of the treating Undersea Medical Officer or cognizant medical provider.

Though specific antibiotic regimens will not be required certain principles should be kept in mind (29). Therapy should not be given unless the clinician has a positive result for *H. pylori*. In fact, if a patient presents with an *H. pylori* negative ulcer it may indicate an unusual and possibly more serious disorder such as the Zollinger-Ellison syndrome (52). Treatments longer than 14 days have a higher likelihood of creating drug resistant bacteria and have not been associated with higher success rates (29). Longer and more complicated treatment regimens tend to decrease compliance. This has the effect of increasing the likelihood of developing drug resistance and treatment failures.

If therapy fails the same drug regimen should not be used again. *H. pylori* resistance to metronidazole and clarithromycin develops readily therefore these agents should not be used twice. Following therapy, a four week antibiotic and antisecretory free period should be observed prior to any additional diagnostic testing to confirm eradication.

A treatment regimen will not be recommended but a brief description of the current FDA approved options can be found in Table 5 (73). A summary of other treatment options as described in the 1996 Consensus Statement for the Medical Treatment of Peptic Ulcer Disease is presented in Tables 6 and 7 (14, 74-77). A comparison of the two tables should make apparent why a standard treatment regimen will not be required. As *H. pylori* develops resistance and as new antibiotics are developed it appears prudent to remain flexible as to which therapy is used by the clinician.

Conclusions:

The recent advances in understanding the etiology of PUD and improved disease management argued for relaxation of the US Navy's disqualification policy. It is now widely accepted that *H. pylori* infection is the cause of the majority of PUD cases. When *H. pylori* is eliminated with common antibiotics, dramatic and persistent reduction in ulcer recurrence rate and associated complications occur. The low recurrence rate of PUD following eradication of *H. pylori* increases the predictability of the disease and strongly suggests that the disqualification period can be significantly shortened with minimal risk to either the patient or submarine mission. It was therefore proposed that submariners with PUD be allowed to return to duty no less than two months after successfully completing treatment. Successful treatment is determined by complete healing of all lesions confirmed by endoscopy and evidence of *H. pylori* eradication demonstrated by negative culture or the ¹³C urease breath test.

Appendix A is the Naval Submarine Medical Research Laboratory's recommended guidance for disposition of submariners with peptic ulcer disease. This recommendation was accepted and distributed to the fleet as Appendix XVIII of the COMSUBLANT/PAC INSTRUCTION 6000.2B CHANGE TRANSMITTAL TWO dated 20OCT97.

In order to minimize the risks and quantify the outcome of returning submariners back to duty following ulcer healing, a prospective study following those submariners was suggested. A study examining the prevalence of *H. pylori* in the USN submarine force (currently being done at the Naval Submarine Medical Research

Laboratory) would further clarify the PUD risk factors a waived submariner is exposed to upon return to duty. By accepting a change in the USN's policy regarding PUD, an effort to maintain pace with current medical treatment outcomes was established.

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APPENDIX A
NSMRL'S RECOMMENDED GUIDANCE
FOR DISPOSITION OF SUBMARINERS WITH PUD

The following section presents the new guidance for returning submariners back to duty following PUD. The bold boxed print is the actual proposed element of the guidance and the text following the box is commentary.

1. ESTABLISH DIAGNOSIS: Document diagnosis and infection by endoscopy with biopsy/culture, or CLO test. Perform a ¹³C urease breath test.

The first step in any waiver process is to accurately diagnose and characterize the illness in question. The standard of care for diagnosing and treating peptic ulcer disease is summarized in figure 1 and table 3. (14, 27, 29, 30). In order to positively diagnose PUD and assess whether the subject is *H. pylori* positive an endoscopy is required. Endoscopy is very sensitive and specific in diagnosing ulcers. Biopsy tissue for malignant ulcers and to culture for *H. pylori* (or for a CLO test) is also accessible via endoscopy. As the sensitivity and specificity of tissue culture and CLO test are both very high either is considered acceptable.

In order to prospectively follow the waived submariners and determine ulcer recurrence rate a recently FDA approved ¹³C urease breath test will be performed yearly. This test was chosen because it can globally test for *H. pylori* in the stomach, is safe, easy to administer, and is non-invasive. The initial breath test will serve as a baseline for future reference.

2. ADMINISTER APPROPRIATE TREATMENT: Several acceptable regimens are available and as studies continue and drug resistance's change, treatment recommendations will evolve. Therefore, no specific regimen is prescribed. The appropriate regimen will be at the discretion of the treating gastroenterologist and consistent with current clinical guidelines.

Currently there are a number of recommended and highly effective drug regimens available to treat *H. pylori* infected people (1, 14). Because drug resistance evolves and drug regimens change, a specific antibiotic recommendation will not be made. As long as the standard of care is followed and the *H. pylori* infection is eradicated, the specific medications used will be up to the discretion of the treating Undersea Medical Officer or cognizant medical provider.

3. VERIFY ERADICATION: A minimum of 4 weeks following completion of treatment, document via repeat endoscopy (with either biopsy or CLO test) and urease breath test both complete healing of the ulcer and eradication of the *H. pylori* infection. Serological testing typically shows decreasing titers over several months in individuals who have been successfully treated, but its variability precludes reliable determination of *H. pylori* eradication.

To remain conservative and accurately verify ulcer healing and *H. pylori* eradication a repeat endoscopy, biopsy and culture, and urease breath test will be performed. Most uncomplicated ulcers (80%) heal in 4 to 8 weeks (2), therefore the minimum amount of time prior to documenting ulcer and *H. pylori* cure should be 4 weeks.

Serum antibody titers are not useful because the decline following successful eradication is slow, variable in magnitude, and not reliable (30, 78). Therefore the urease breath test, which is only positive when urease producing organisms reside in the gut, is required.

4. INITIAL DISPOSITION:

a. Individuals in whom infection is not eradicated or ulcer has not healed

- 1. Provide treatment as medically appropriate**
- 2. Process for submarine duty disqualification**

b. Individuals in whom infection is eradicated and ulcer has healed

- 1. Submit request for waiver. Waiver will be conditioned upon no recurrence of ulcer and compliance with prescribed treatments and follow-ups.**
- 2. Instruct the patient to avoid non-steroidal anti-inflammatory drug use unless prescribed by a physician aware of his peptic ulcer disease history.**
- 3. Instruct patient to promptly report any recurrence of symptoms to the medical department representative and cognizant Undersea Medical Officer.**
- 4. Follow-up annually with interval history, a urease breath test, and additional examinations or tests as clinically indicated.**

Four weeks following treatment for both the *H. pylori* organism and PUD, and after repeat endoscopy and *H. pylori* testing has been performed, the submariners disposition must be considered. For refractory ulcers (nonhealing of ulcer following three months of appropriate therapy (1)), or organisms unable to be eradicated, the submariner remains in either a continued disqualified state (refractory ulcer) or is a high risk for recurrence (continued *H. pylori* infection). With either of these situations the submariner will be disqualified according to the current guidelines (79). Currently he would be eligible for a waiver following a two year ulcer-free period.

If the ulcer and *H. pylori* is eradicated, a waiver must be submitted to COMSUBLANT or COMSUBPAC and then forwarded to BUMED. As a condition of the waiver the subject must be counseled to avoid indiscriminate use of non-steroidal anti-inflammatory agents that may

increase risk of developing ulcers in susceptible individuals. The submariner is to report any peptic ulcer symptoms (hematemesis, gnawing epigastric pain, or symptoms similar to those with the initial ulcer).

5. FOLLOW-UP: Successfully treated individuals require annual urease breath test and evaluation by an Undersea Medical Officer with emphasis placed on identification of symptom recurrence. A positive urease breath test does not necessarily require further study but should prompt a thorough search for symptoms. Other diagnostic testing will be performed as clinically indicated. Asymptomatic individuals do not require annual endoscopy or imaging. Individuals with recurrent ulcer should be provided appropriated treatment and processed for submarine disqualification.

Given the evidence that ulcer recurrence is associated with *H. pylori* re-infection it is prudent to track those individuals shown by their history to be prone to developing an ulcer. In order to track waived individuals a mandatory annual follow up will be required. Asymptomatic individuals will be required to have documented evidence of a symptom-free interim history, absence of physical signs, and a negative *H. pylori* ¹³C urease breath test. Endoscopy and imaging will not be required. Endoscopy is indicated in those individuals exhibiting or suspected of having an ulcer. Disposition of submariners with positive *H. pylori* tests will be up to the Undersea Medical Officer's discretion.

An annual follow-up test for *H. pylori* is indicated as the relationship between *H. pylori* re-infection and ulcer recurrence is presently unknown, the mode of transmission is undetermined at this time, the prevalence of *H. pylori* in the USN submarine fleet is unknown, and there is a 1% chance of those infected with *H. pylori* progressing to peptic ulcer disease. The ¹³C urease breath test has been chosen as the annual test for *H. pylori* because it tests for the presence of active and current infection with *H. pylori*. Serum tests, as previously mentioned, are variable in magnitude and not reliable (30, 78). Furthermore, serum antibody tests remain positive in the face of *H. pylori* eradication because antibodies to the bacteria remain in the bloodstream.

6. NAVAL SUBMARINE MEDICAL RESEARCH LABORATORY STUDY:

The Naval Submarine Medical Research Laboratory (NSMRL) has designed a research protocol to scientifically evaluate recurrence rate and risk factors among submariners who are granted waivers for PUD caused by *H. pylori* which has been successfully eradicated. The protocol parallels the procedure outlined above, but in no way is the individual to be given the impression that the waiver is contingent on his consent to participate in the NSMRL study. Participation in the study should be offered only after the individual has been granted a waiver.

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 074-0188	
1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF THE REPORT Approved for public release; distribution unlimited		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) NSMRL REPORT 1210			5. MONITORING ORGANIZATION REPORT NUMBER(S) NA		
6a. NAME OF PERFORMING ORGANIZATION Naval Submarine Medical Research Laboratory		6b. OFFICE SYMBOL (if Applicable)	7a. NAME OF MONITORING ORGANIZATION Naval Medical Research and Development Command		
6c. ADDRESS (City, State, Zip Code) Box 900, Naval Submarine Base NLON, Groton, CT 06349-5900			7b. ADDRESS (City, State, Zip Code) 8901 Wisconsin Avenue Bethesda, MD 20889-5606		
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Same as 7a.		8b. OFFICE SYMBOL (if Applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER		
8c. ADDRESS (City, State, Zip Code) Same as 7b			10. SOURCE OF FUNDING NUMBERS		
			PROGRAM ELEMENT NO 63706N	PROJECT NO. M0096	TASK NO. 002
					WORK UNIT ACCESSION
TITLE (Include Security Classification) A New Strategy to Address Loss of Submarine Qualifications in Submariners Who are <i>Helicobacter Pylori</i> Positive and Diagnosed with Peptic Ulcer Disease: Background to the Change in Policy					
Personal Author(s) C. C. Steevens, R. Syl.vester, J. Clark					
13a. TYPE OF REPORT Interim		13b. TIME COVERED FROM TO		DATE OF REPORT (Year, Month, Day) 1998 August 25	
				PAGE COUNT 23	
SUPPLEMENTARY NOTATION					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP			
ABSTRACT (Continue on reverse if necessary and identify by block number)					
DISTRIBUTION/AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS REPORT <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION		
22a. NAME OF RESPONSIBLE INDIVIDUAL E. Perkins			22b. TELEPHONE (Include Area Code) (860) 694-3263		22c. OFFICE SYMBOL